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Phase 2 study of carfilzomib, thalidomide, and low-dose dexamethasone as induction and consolidation in newly diagnosed, transplant eligible patients with multiple myeloma, the carthadex trial

by Ruth Wester, Bronno van der Holt, Emelie Asselbergs, Sonja Zweegman, Marie Jose Kersten, Edo Vellenga, Marinus van Marwijk Kooy, Okke de Weerd, Monique Minnema, Sarah Lonergan, Antonio Palumbo, Henk Lokhorst, Annemiek Broijl, and Pieter Sonneveld

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Title: Phase 2 study of carfilzomib, thalidomide, and low-dose dexamethasone as induction and consolidation in newly diagnosed, transplant eligible patients with multiple myeloma, the carthadex trial

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Abstract

This is a phase 2 dose escalation trial of carfilzomib in combination with thalidomide and dexamethasone for induction and consolidation in transplant-eligible patients with newly diagnosed multiple myeloma. The results of 4 dose levels are reported. Induction therapy consisted of 4 cycles of carfilzomib 20/27 mg/m² (n=50), 20/36 mg/m² (n=20), 20/45 mg/m² (n=21) and 20/56 mg/m² (n=20) on days 1, 2, 8, 9, 15, 16 of a 28-day cycle; thalidomide 200 mg on day 1 through 28 and dexamethasone 40 mg weekly. Induction therapy was followed by high dose melphalan and autologous stem cell transplantation and consolidation therapy with 4 cycles of carfilzomib, thalidomide and dexamethasone in the same schedule except a lower dose of thalidomide (50 mg).

Very good partial response rate or better and complete response rate or better after induction therapy were 65% and 18% respectively, increasing to 86% and 63% respectively after consolidation therapy. In all cohorts combined, after a median follow-up of 58.7 months, median progression-free survival was 58 months (95% CI 45-67 months). Median overall survival was 83 months (95% CI 83 months-not reached). Grade 3/4 adverse events consisted mainly of infections, respiratory disorders, skin and vascular disorders in 11%, 8%, 9%, and 9% respectively. Only in 1 patient grade 3 polyneuropathy was reported. Cardiac events were limited, grade 3/4 in 5% of patients. Carfilzomib, thalidomide and dexamethasone as induction and consolidation treatment after high dose melphalan and autologous stem cell transplantation is highly efficacious and safe in transplant-eligible patients with newly diagnosed multiple myeloma. This study was registered at <http://www.trialregister.nl> as #NTR2422.

Introduction

Survival rates in patients with multiple myeloma (MM) have significantly improved during the last decades. However, eventually the majority of patients progress and the need for new therapeutic approaches remains. In transplant-eligible patients with newly diagnosed multiple myeloma (NDMM), depth of response before and after high-dose melphalan/autologous stem cell transplantation (HDM/ASCT) is associated with improvement in progression-free survival (PFS) and overall survival (OS).(1-5) Therefore, it is important to select the appropriate induction and consolidation therapy in order to achieve a maximum response after ASCT and to maintain or even increase this response during consolidation therapy and thereafter.

Standard induction treatment consists of triple therapy including a proteasome inhibitor, and/or an immunomodulatory drug and dexamethasone. The combination of bortezomib, thalidomide and dexamethasone (VTD) has been extensively investigated in transplant-eligible patients with NDMM.(6-8) However, treatment with bortezomib is associated with higher rates of polyneuropathy (PN) and consequently discontinuation of treatment.(7, 8) It is important to use a regimen that is highly effective and safe in patients with NDMM. This could improve treatment adherence and subsequently outcome after induction and consolidation therapy.

Carfilzomib is a selective proteasome inhibitor with irreversible binding to the constitutive proteasome and immunoproteasome. It is approved in the United States and in Europe as a single-agent for the treatment of patients with relapsed and/or refractory MM (RRMM).

Carfilzomib is approved at a dose of 27 mg/m² in combination with lenalidomide and dexamethasone in RRMM based on the data from the ASPIRE trial showing a superior PFS of median 26.3 months vs 17.4 months when patients were treated with lenalidomide/dexamethasone.(9) Carfilzomib is also approved at a dose of 56 mg/m² in combination with dexamethasone, based on data from the ENDEAVOR trial showing a superior PFS over bortezomib/dexamethasone of median 18.7 months vs 9.4 months (p<0.0001).(10)

Previous trials showed that the incidence of PN with carfilzomib is lower compared to bortezomib.(9-11)

Carfilzomib is not yet approved for treatment in NDMM in Europe. Recent trials in patients with NDMM, using different treatment regimens, showed high response rates.(12-15) A phase 1/2 trial of patients with NDMM treated with carfilzomib at a maximum dose of 36 mg/m² combined with lenalidomide and low-dose dexamethasone showed a very good partial response (VGPR) rate of 81%. PFS at 24 months was 92%.(12)

We have previously initiated a Phase 2 dose-escalation trial of carfilzomib combined with thalidomide and dexamethasone. The combination of a proteasome inhibitor and an immunomodulating agent has a proven synergistic effect.(6) Moreover, thalidomide is an effective and affordable drug available in many countries.

In NDMM no consensus exists about the optimum dose level of Carfilzomib, implicating the need for dose finding trials. Goal of this trial was to investigate the efficacy of this combination at various dose levels of carfilzomib in NDMM. Results of the first three cohorts of this Carthadex trial have been published in 2015.(11) Overall response rate (ORR) after induction therapy was 90% with a VGPR rate of 68%. PFS at 36 months was 72%. The combination of carfilzomib, thalidomide and dexamethasone (KTd) was well tolerated.(11). Four different dose levels were included in this trial based on the hypothesis that a higher dose level induces a higher response rate.(12, 16) We report herein the results of our dose escalation cohorts with long follow-up. This is the first study using KTd for both induction and consolidation therapy and comparing different dose levels.

Methods

Patients

Transplant-eligible patients with NDMM, aged 18 to 65 years, could be enrolled. Patients were required to have a World Health Organization (WHO) performance status of 0 to 3 (WHO 3 was allowed only when caused by MM and not by co-morbid conditions).

Patients were ineligible if they had grade 3/4 polyneuropathy (PN) or grade 2 painful PN, severe cardiac dysfunction (New York Heart Association class II to IV), known intolerance of thalidomide, systemic amyloid light-chain amyloidosis, non-secretory MM, Waldenström macroglobulinemia or IgM MM, creatinine clearance < 15 mL/min, absolute neutrophil count < $1.0 \times 10^9/L$, platelets < $75 \times 10^9/L$, hemoglobin < 4.9 mmol/L, active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma.

This independent investigator-initiated multi-institutional study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the European Clinical Trial Directive as implemented in Dutch law.

The protocol was approved by institutional review boards and ethics committees. All patients signed an informed consent.

Study design and treatment

This single-arm, open-label, phase 2 trial was conducted at 8 hematology centers. Patients were treated with 4 cycles KTd of a 28-day cycle for induction therapy. Carfilzomib was administered in a 30 minutes infusion. The dose in the first dosing cohort was 20 mg/m² on days 1 and 2 and was escalated to a dose of 27 mg/m² on days 8, 9, 15 and 16 of cycle 1 and on days 1, 2, 8, 9, 15 and 16 of cycles 2 to 4. Thalidomide 200 mg was given orally on days 1 through 28 and dexamethasone 40 mg was given orally on days 1, 8, 15 and 22. Induction therapy was followed by stem cell harvest after Cyclophosphamide priming (2 to 4 mg/m² IV) and daily 10 µg/kg granulocyte colony-stimulating factor. Hereafter patients received high-dose

Melphalan (HDM, 200mg/m²) and ASCT followed by consolidation treatment with 4 cycles of KTD in the same schedule and dose as induction treatment except that the dose of thalidomide was 50 mg instead of 200 mg. The dose of carfilzomib was escalated to 20/36 mg/m², 20/45 mg/m² and 20/56 mg/m² in cohort 2, 3 and 4 respectively. During the study protocol patients were required to maintain adequate hydration. In addition, patients were treated prophylactically with antibiotics (ciprofloxacin or another fluoroquinolone) and with antiviral medication (acyclovir or a similar anti varicella agent). All patients received antithrombotic prophylaxis with aspirin in case of low thrombotic risk or with low-molecular-weight heparin in patients with pre-existing thrombotic risk factors.(17)

The primary endpoint of the study was response after induction therapy and overall response, specifically complete response (CR) and VGPR. Secondary endpoints were efficacy and safety, maximum tolerated dose (MTD), dose limiting toxicities (DLT), PFS and overall survival (OS). PFS was defined as time from registration to progression or death, whichever came first. OS was calculated from registration to death from any cause; patients still alive at last contact were censored.

This study was registered at <http://www.trialregister.nl> as #NTR2422.

Assessments

Treatment responses and disease progression were assessed by study investigators and were classified according to International Myeloma Working Group (IMWG) Uniform Response Criteria, with categories for CR, VGPR, and partial response (PR).(18) Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 4.0.(19) Bone marrow analysis was performed at diagnosis to quantify myeloma cell involvement. Molecular, cytogenetic and fluorescence in situ hybridization studies were performed on these samples. CD138+ purified MM cells were used to determine the presence of the following cytogenetic abnormalities: t(4;14)(p16;q32), t(14;16)(q32;q32), del(13q),

del(17p), 1p/q abnormalities, numerical abnormalities of chromosome 9 or 11, and complex cytogenetic abnormalities.(11)

Statistical analysis

This study was designed to investigate whether induction treatment with KTd warrants further investigation in future trials. The intention-to-treat principle was used for all analyses, restricted to eligible patients. A CR + VGPR rate lower than 25% after induction treatment, was considered too low to warrant further investigation in future trials, however if the CR + VGPR rate was higher than 45% therapeutic activity was considered sufficiently high to support further investigation. To reject the null hypothesis in favor of the alternative hypothesis with power $1 - \beta = 0.80$ (2-sided significance level $\alpha = 0.05$), a minimum of 41 patients should be included. A 95% confidence interval (CI) was constructed around the CR + VGPR rate after induction treatment and the null hypothesis was rejected if the lower boundary was larger than 25%. Predefined subgroup analyses were performed to investigate the effect of risk status, using cytogenetic/fluorescence in situ hybridization criteria, ISS stage and R-ISS stage, on response and survival. In this trial patients were considered to be high-risk if they had t(4;14) and/or del(17p) and/or add(1q) and/or ISS stage III.

Continuous and categorical data were summarized with descriptive statistics. Survival end points were estimated using the Kaplan-Meier method, and 95% CI were constructed. The log-rank was used to evaluate differences in PFS and OS between subgroups. Statistical analysis was performed using Stata v15.1 software (StataCorp, College Station, TX).

Results

Patients and treatment

One hundred and eleven patients were enrolled between September 16, 2010 and December 30, 2013. The analysis was based on data available as of February 27, 2018 with a median follow-up of 58.7 months (range 25.1-88.0 months). Four different dose levels were investigated (27mg/m² n=50, 36 mg/m² n=20, 45 mg/m² n=21 and 56 mg/m² n=20). Baseline demographics and disease characteristics are shown in table 1. Median age was 58 years with a range of 29 to 66 years and the male/female distribution 61/39%. Nine percent of patients had an R-ISS stage 3 and in 9% of patients R-ISS stage was unknown mainly due to missing cytogenetics. A total of 39% of patients were classified as high-risk based on cytogenetics and ISS stage, 41% of patients were classified as standard risk. In 20% of patients risk status was unknown, mainly due to missing cytogenetics. Seven patients had a history of grade 1/2 PN and two patients a grade 3 PN at diagnosis, whereas in 9 patients baseline assessment of PN was missing at enrollment. A total of 5% of patients had renal insufficiency with a creatinine \geq 177 μ mol/L at diagnosis.

All 111 patients started induction therapy with KTd (figure 1). Six patients discontinued treatment because of the following adverse events (AEs): grade 3 rash (carfilzomib 27 mg/m²), grade 2 fever with sepsis (carfilzomib 27 mg/m²), grade 1 hyponatremia (carfilzomib 27 mg/m²), grade 2 exanthema (carfilzomib 27 mg/m²), grade 3 congestive heart failure (carfilzomib 27 mg/m²), grade 3 pneumonitis (carfilzomib 36 mg/m²), grade 3 drug reaction with eosinophilia and systemic symptoms (Dress syndrome) (carfilzomib 56 mg/m²). One patient appeared not eligible for further treatment and two patients discontinued treatment due to progressive disease. 102/111 patients (92%) continued treatment with high dose cyclophosphamide and stem cell collection. Stem cell collection was successful in 100 of 102 patients with a median CD34+ yield of 5.5×10^6 . A total of 98 patients (88%) continued treatment with a single HDM

(200 mg/m²) and ASCT. Four patients were not eligible for HDM, one because of insufficient CD34+ yield and three because of progression of disease after stem cell collection. After treatment with HDM and ASCT 94 patients (85%) initiated consolidation therapy. Four patients were not eligible for consolidation treatment because of progression of disease (n=1), a delayed hematologic recovery after ASCT (n=1), non-related disease (n=1) and uncontrolled pain after ASCT (n=1). Nine patients discontinued consolidation treatment because of progressive disease (n=2), thrombotic thrombocytopenic purpura (TTP) (n=1), a TTP like syndrome (n=1), overall worsening of condition (n=1), grade 3 fatigue (n=1), refusal of further treatment (n=2) and persisting PNP (n=1). A total of 83 patients (75%) completed all 4 consolidation cycles.

Efficacy

Table 2 shows response to induction, HDM/ASCT and consolidation therapy. Response according to risk group and R-ISS is shown in table 3. Overall response after induction therapy in all 111 patients was 93% with a CR rate of 18%. The \geq VGPR rate after induction therapy was 65% (95% CI 55% to 74%) leading to rejection of the null hypothesis, as the 95% CI is above 25%. The \geq VGPR rate increased to 77% after HDM/ASCT and to 86% after consolidation therapy. ORR increased to 94% after consolidation therapy. CR rate after induction therapy between the four different dose levels was comparable and increased after consolidation therapy. In the three highest dose levels CR rate after consolidation therapy was higher in comparison to the lowest dose level (75%, 67% and 65% vs. 56%, respectively, however this was not statistically significant (test for trend, $p=0.39$; chi-square test 27 mg/m² vs 36-56 mg/m², $p=0.16$)). Response after consolidation treatment between standard risk patients and high-risk patients (defined by ISS stage and cytogenetics) was similar with CR rates of 67% vs 58%. Response after consolidation therapy according to R-ISS stage (I,II and III) was comparable with CR rates of 73%, 57% and 60% respectively.

Median PFS in all 111 patients was 58 months (95% CI 45-67 months). Dose level was not

associated with PFS. Median PFS in high-risk patients was worse compared to standard risk patients (42 vs 60 months, $p=0.006$), while a higher R-ISS stage was also associated with a worse PFS ($p=0.04$) (figure 2).

Median OS was 83 months and 5-year OS was 76% (95% CI 66% to 83%) as shown in figure 3.

Dose level and risk status were not associated with OS.

Safety

Any grade hematological toxicity occurred in 15% of patients. Grade 3/4 hematological toxicity occurred in 10% of patients. In dose level 27 mg/m², 36 mg/m², 45 mg/m² and 56mg/m² grade 3/4 hematological toxicity occurred in 12%, 10%, 10% and 10% respectively. Main grade 3/4 non-hematological toxicity consisted of infections, respiratory disorders, skin and vascular disorders in 11%, 8%, 9%, and 9% respectively. There was a gradual increase in grade 3/4 infections from lower to higher doses of carfilzomib; 0%, 5%, 10% and 15% respectively, and consisted mainly of pneumonia (supplementary table 1).

Table 4 summarizes cardiac AEs. Any grade cardiac AEs were reported in 12% of patients after induction therapy (14% in carfilzomib 27mg/m², 15% in carfilzomib 36 mg/m², 19% in carfilzomib 45 mg/m² and 5% in carfilzomib 56mg/m².) These cardiac events consisted mainly of grade 1/2 toxicity (11 out of 15 events). Five (5%) grade 3 cardiac AEs were reported, three in dose level 27 mg/m², one in dose level 45 mg/m² and one in dose level 56 mg/m².

Any grade cardiac AEs increased to 18% after consolidation therapy with no reports of grade 4 AEs in all four dose levels, (18% in carfilzomib 27mg/m², 15% in carfilzomib 36 mg/m², 19% in carfilzomib 45 mg/m² and 15% in carfilzomib 56mg/m².) These cardiac events consisted mainly of grade 1/2 toxicity (14 out of 19 events). Five (5%) grade 3 cardiac AEs were reported.

Nine patients (8%) developed hypertension during treatment (carfilzomib 27 mg/m² n=3, carfilzomib 36 mg/m² n=3, carfilzomib 45 mg/m² n=2, carfilzomib 56 mg/m² n=1), four (4%) of

them had grade 3 toxicity. Five (5%) patients needed antihypertensive treatment.

Seven patients (6%) had preexisting PN grade 1/2 and two patients (2%) had preexisting grade 3 PN. During induction and consolidation therapy 52 patients (47%) developed PN. Grade ≥ 2 PN events occurred in 23 patients (20%) independent from carfilzomib dose and was clinically manageable (carfilzomib 27 mg/m² n=11, carfilzomib 36 mg/m² n=3, carfilzomib 45 mg/m² n=6, carfilzomib 56 mg/m² n=3). Only one patient (1%) reported grade 3 PN (carfilzomib 27mg/m²). At least one Serious AE (SAE) was reported in 43% of patients. In cohort 1 an SAE was reported in 21 (42%) patients, in cohort 2 in 8 (40%) patients, in cohort 3 in 7 (33%) patients and in cohort 4 in 12 (60%) patients.

As shown earlier 9 patients (8%) discontinued treatment protocol due to excessive toxicity, six patients during induction therapy and three patients during consolidation therapy. In cohort 1, four (8%) patients went off protocol due to AEs, one (5%) patient in cohort 2 and four (20%) patients in cohort 4. Table 5 shows an analysis of treatment adherence to protocol. During consolidation treatment normal completion rate for carfilzomib and dexamethasone was similar to induction treatment whereas this was higher for thalidomide, probably due to the lower dose of thalidomide during consolidation treatment. A higher percentage of patients prematurely discontinued treatment at the highest dose level of carfilzomib (5 patients (30%)). Four patients (20%) had excessive toxicity and two patients (10%) requested to discontinue treatment (supplementary table 2).

Discussion

Results of the first 3 dose levels of this phase 2 trial have been published before.(11) In this paper we discuss the results of 4 dose levels of carfilzomib. As shown before, treatment with KTd for induction and consolidation in transplant eligible patients with NDMM is safe, tolerable and effective. We included the additional cohort with the highest dose level of 56 mg/m², based on the hypothesis that a higher dose level induces a higher response rate.(12, 16) Response after induction was high with 65% of patients reaching at least VGPR, increasing to 86% after consolidation therapy. CR rate after consolidation was high with 63%. Response (i.e. >CR) after consolidation in the higher three dose levels (20/36, 20/45, 20/56) was better than in the lowest dose level (20/27) however, the small sample size and the non-randomized design of the study preclude firm conclusions about superiority of the highest dose levels. In the ARROW trial, 478 patients with RRMM were randomized between treatment with carfilzomib twice a week 27 mg/m² or once weekly 70 mg/m². PFS was higher with once weekly 70 mg/m² than with twice weekly 27 mg/m² (11.2 months vs 7.6 months).(20) These data and our data (based on response) suggest that a dose of at least 36 mg/m² twice weekly (which equals 70 mg/m² once weekly), would be the preferred dose.

An important remaining question relates to the efficacy of this regimen in high-risk patients. In this trial with limited numbers, the negative impact of high-risk cytogenetics was not abrogated by carfilzomib.(21) At the same time, overall risk status, based on cytogenetics and ISS stage, was not significantly associated with response. However, high-risk patients and patients with a higher R-ISS score had a significantly worse PFS. Median PFS and OS for all patients were 58 months and 83 months, respectively. These data show that treatment with KTd is effective as frontline treatment of transplant eligible patients with NDMM. Also, this regimen had no effect on stem cell mobilization and collection, with the exception of 2 patients in whom stem cell collection failed. Several phase 2 trials have investigated treatment with carfilzomib in NDMM using different regimens.(12-15) In the CYKLONE trial cyclophosphamide was added to the KTd

regimen. They showed a comparable ORR of 91% and a PFS at 24 months of 76%. In this study MTD was 20/36 mg/m².(13) In comparison, in the Carthadex trial dose levels of 45 mg/m² and 56 mg/m² were well tolerated without additional toxicity compared to dose levels 27 mg/m² and 36 mg/m². The number of patients going off treatment due to excessive toxicity was low, 9 out of 111 patients (8%). Our data show that efficacy and safety are comparable at dose levels 36 mg/m² and upward. Main grade 3/4 non-hematological toxicity consisted of infections, respiratory disorders, skin and vascular disorders. The rate of cardiac AEs was low in this trial. Five patients (5%) experienced grade 3 cardiac AE, including congestive heart failure, dyspnea and chest pain. This is comparable to other trials investigating carfilzomib in NDMM.(12-14) The rate of grade 3/4 cardiac toxicity is slightly higher in RRMM, most likely because patients are older and due to previous treatment.(9, 10) However, the limited number of patients preclude firm conclusions about safety regarding cardiac events between the different dose levels. Jakubowiak et al. performed a phase 1/2 trial of carfilzomib combined with lenalidomide and dexamethasone (CRd). In this trial patients not proceeding to ASCT continued treatment with CRd beyond 8 cycles with a median of 12 cycles. PFS at 24 months was 92%.(12) However, thalidomide remains a valuable and available treatment option in many countries, due to availability and due to low costs, and offers a great alternative to treatment with lenalidomide. Recently several trials have been performed in patients with NDMM, using alternative schedules for induction and consolidation. The Intergroupe Francophone du Myélome (IFM) performed a phase 2 trial of lenalidomide combined with bortezomib and dexamethasone (RVD) for induction and consolidation. PFS at 3 years was 77% and CR rate was 58%. Most common toxicities were grade 1/2 PN in 55%.(22) In the EMN02 trial VCD for induction was followed by VRD for consolidation treatment. CR rate was 55% and PFS not reached at 60 months.(23) Although it should be taken into account that this is a cross comparison between trials, the Carthadex trial efficacy data are similar with median PFS of 58 months and CR rate of 63% and acceptable toxicity. Moreover, the combination of carfilzomib, thalidomide and dexamethasone

is an affordable treatment regimen. These data suggest that CTd is an effective and safe induction and consolidation regimen in newly diagnosed MM.

In conclusion, the combination of carfilzomib, thalidomide and low-dose dexamethasone appears highly efficacious and safe in transplant-eligible patients with NDMM across all dose levels with manageable toxicities. Consolidation therapy after ASCT results in a major improvement in response. In addition, we observed that higher dose levels of carfilzomib (36 to 56 mg/m²) result in better response rates after consolidation therapy. Current studies in newly diagnosed multiple myeloma patients are performed using 36 mg/m² twice weekly. 36 mg/m² twice weekly (or 70 mg/m² once weekly) will be the preferred dose to be used in practice, which we would recommend based on our carthadex response data. Results of cohort 5 in which patients were treated with 8 instead of 4 induction cycles will follow in the near future. Further randomized, prospective studies are needed to confirm these data and determine the position of carfilzomib in the treatment of patients with NDMM.

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Tables:

Table 1: Baseline characteristics

Characteristic	20/27 mg/m ²	20/36 mg/m ²	20/45 mg/m ²	20/56 mg/m ²	All patients
Patients, n	50	20	21	20	111
Male, n (%)	34 (68)	11 (55)	16 (76)	7 (35)	68 (61)
Age, median (range), years	58 (29-66)	58 (47-64)	56 (33-65)	58 (37-65)	58 (29-66)
ISS stage, n (%)					
1	18 (36)	5 (25)	14 (67)	9 (45)	46 (41)
2	20 (40)	7 (35)	4 (19)	7 (35)	38 (34)
3	12 (24)	8 (40)	2 (10)	4 (20)	26 (23)
Unknown	0 (0)	0 (0)	1 (5)	0 (0)	1 (1)
R-ISS stage, n (%)					
1	7 (14)	3 (15)	10 (48)	6 (30)	26 (23)
2	37 (74)	10 (50)	7 (33)	11 (55)	65 (59)
3	2 (4)	5 (25)	0 (0)	3 (15)	10 (9)
Unknown	4 (8)	2 (10)	4 (19)	0 (0)	10 (9)
WHO performance status, n (%)					
0	24 (48)	7 (35)	11 (52)	12 (60)	54 (49)
1	20 (40)	10 (50)	7 (33)	8 (40)	45 (41)
2	2 (4)	1 (5)	1 (5)	0 (0)	4 (4)
3	0 (0)	0 (0)	2 (10)	0 (0)	2 (2)
Unknown	4 (8)	2 (10)	0 (0)	0 (0)	6 (5)
M-protein isotype, n (%)					
IgA	11 (22)	5 (25)	4 (19)	4 (20)	24 (22)
IgG	30 (60)	8 (40)	10 (48)	11 (55)	59 (53)
IgD	1 (2)	1 (5)	1 (5)	0 (0)	3 (3)
Light-chain disease	7 (14)	4 (20)	6 (29)	5 (25)	22 (20)
Unknown	1 (2)	2 (10)	0 (0)	0 (0)	3 (3)
Genetic abnormalities, n (%)*					
add 1q					
Yes	5 (10)	4 (20)	2 (10)	7 (35)	18 (16)
No	35 (70)	12 (60)	15 (71)	10 (50)	72 (65)
Unknown	10 (20)	4 (20)	4 (19)	3 (15)	21 (19)
t(4;14)(p16;32)					
Yes	2 (4)	2 (10)	0 (0)	3 (15)	7 (6)
No	39 (78)	14 (70)	19 (90)	13 (65)	85 (77)
Unknown	9 (18)	4 (20)	2 (10)	4 (20)	19 (17)
del(17p13)					
Yes	3 (6)	2 (10)	1 (5)	1 (5)	7 (6)
No	38 (76)	14 (70)	18 (86)	16 (80)	86 (77)
Unknown	9 (18)	4 (20)	2 (10)	3 (15)	18 (16)
t(11;14)(q13;q32)					

Yes	5 (10)	1 (5)	2 (10)	1 (5)	9 (8)
No	36 (72)	15 (75)	17 (81)	15 (75)	83 (75)
Unknown	9 (18)	4 (20)	2 (10)	4 (20)	19 (17)
t(14;16)(q32;q23)					
Yes	3 (6)	1 (5)	0 (0)	0 (0)	4 (4)
No	38 (76)	15 (75)	19 (90)	16 (80)	88 (79)
Unknown	9 (18)	4 (20)	2 (10)	4 (20)	19 (17)
Risk status, n (%)†					
High	19 (38)	10 (50)	4 (19)	10 (50)	43 (39)
Standard	21 (42)	6 (30)	12 (57)	7 (35)	46 (41)
Unknown	10 (20)	4 (20)	5 (24)	3 (15)	22 (20)
Grade 1/2 PNP, n (%)‡	3 (6)	2 (10)	0 (0)	2 (10)	7 (7)

PNP, polyneuropathy. *A total of 93 patients were evaluable. The table shows the presence of the genetic abnormality in all four dose levels together and in each dose level separately. †High-risk: t(4;14) and/or 17p- and/or add1q cytogenetic abnormalities and/or ISS stage 3 disease. Standard risk: the remaining patients with available cytogenetics and ISS stage. ‡Not recorded in 9 patients.

Table 2: Response after induction, after HDM and after consolidation therapy.

Dosing level carfilzomib	20/27 mg/m ²	20/36 mg/m ²	20/45 mg/m ²	20/56 mg/m ²	All patients
Patients, n	50	20	21	20	111
Response after induction, n (%)					
sCR	4 (8)	1 (5)	0 (0)	1 (5)	6 (5)
≥ CR	8 (16)	5 (25)	3 (14)	4 (20)	20 (18)
≥ VGPR	27 (54)	16 (80)	13 (62)	16 (80)	72 (65)
≥ PR	45 (90)	20 (100)	20 (95)	18 (90)	103 (93)
Response after HDM, n (%)					
sCR	5 (10)	2 (10)	3 (14)	1 (5)	11 (10)
≥ CR	12 (24)	7 (35)	9 (43)	6 (30)	34 (31)
≥ VGPR	32 (64)	17 (85)	19 (90)	18 (90)	86 (77)
≥ PR	46 (92)	20 (100)	20 (95)	18 (90)	104 (94)
Response after consolidation, n (%)					
sCR	17 (34)	4 (20)	8 (38)	4 (20)	33 (30)
≥ CR	28 (56)	15 (75)	14 (67)	13 (65)	70 (63)
≥ VGPR	40 (80)	18 (90)	20 (95)	18 (90)	96 (86)
≥ PR	46 (92)	20 (100)	20 (95)	18 (90)	104 (94)

sCR, stringent complete remission. CR, complete remission. VGPR, very good partial response. PR, partial response

Table 3: Response after consolidation therapy according to risk status and R-ISS

	Standard risk*	High-risk*	R-ISS 1	R-ISS 2	R-ISS 3	Total
Patients, n	46	43	26	65	10	111
sCR, n (%)	16 (35)	9 (21)	10 (38)	19 (29)	0 (0)	33 (30)
≥ CR, n (%)	31 (67)	25 (58)	19 (73)	37 (57)	6 (60)	70 (63)
≥ VGPR, n (%)	40 (87)	36 (84)	24 (92)	54 (83)	9 (90)	96 (86)
≥ PR, n (%)	44 (96)	38 (88)	26 (100)	58 (91)	10 (100)	104 (94)

*High-risk: t(4;14) and/or 17p- and/or add1q cytogenetic abnormalities and/or ISS stage 3 disease. Standard risk: the remaining patients with available cytogenetics and ISS stage.

Table 4: Cardiac adverse events between dose levels

	20/27 mg/m ² , n=50		20/36 mg/m ² , n=20		20/45 mg/m ² , n=21		20/56 mg/m ² , n=20	
Cardiac toxicity, n (%)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Acute coronary syndrome	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Atrial flutter	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Atrial fibrillation	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Angina pectoris	3 (6)	0 (0)	1 (5)	0 (0)	2 (10)	1 (5)	1 (5)	0 (0)
Congestive heart failure	1 (2)	2 (4)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Dyspnea	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Palpitations	1 (2)	0 (0)	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)
Pericardial fluid	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Total of cardiac events	7 (14)	3 (6)	4 (20)	0 (0)	3 (14)	1 (5)	1 (5)	1 (5)

Table 4. Cardiac adverse events during induction and consolidation between dose levels.

Table 5. Adherence to treatment protocol during induction and consolidation

Kolom1	Induction (N=111)	Consolidation (N=94)
Carfilzomib		
Normal completion	68 (61)	61 (55)
Dose delay, reduction and/or interruption	37 (33)	24 (22)
Premature stop	6 (5)	9 (10)
Thalidomide		
Normal completion	54 (49)	63 (67)
Dose delay, reduction and/or interruption	42 (38)	8 (9)
Premature stop	15 (14) (a)	23 (24) (b)
Dexamethasone		
Normal completion	85 (77)	66 (70)
Dose delay, reduction and/or interruption	20 (18)	18 (19)
Premature stop	6 (5)	10 (11)

(a) Including 9 patients who received no thalidomide during induction cycle 4. (b) Including 14 patients who received no thalidomide during consolidation cycle 4

Figures

Figure 1: Consort diagram

Figure 1: Cyclo, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; HD, high dose; SC, stem cell

Figure 2. Progression-free survival

Figure 2. Kaplan-Meier curve of progression-free survival (PFS). (A) PFS in all 111 patients. (B) PFS per dose level. (C) PFS according to risk status. (D) PFS according to R-ISS.

Figure 3. Overall survival.

Figure 3. Kaplan-Meier curve overall survival (OS). (A) OS in all 111 patients. (B) OS per dose level. (C) OS according to risk status. (D) OS according to R-ISS.

Figure 1

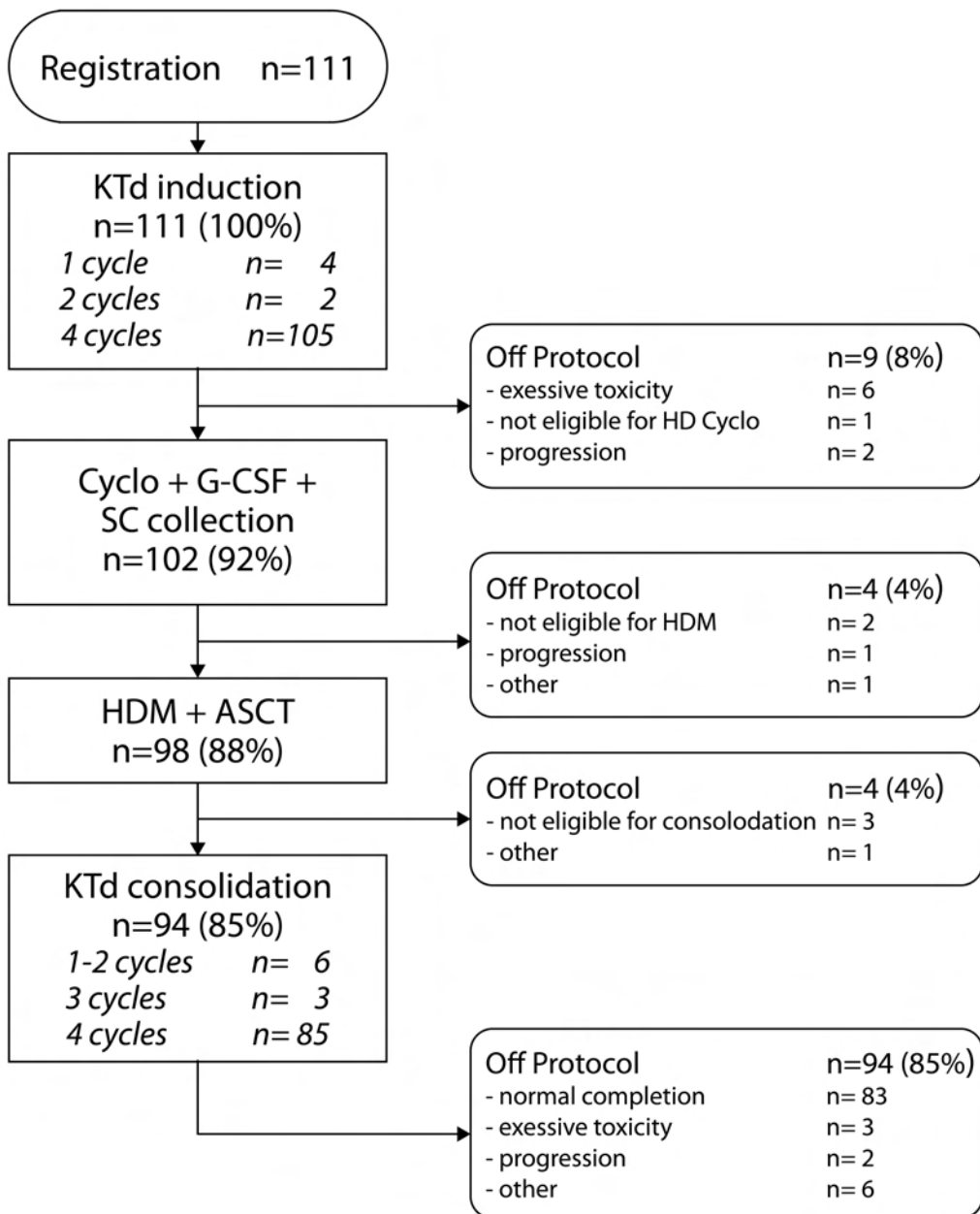


Figure 2

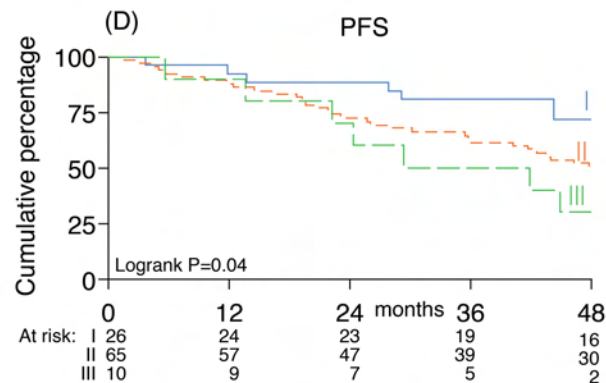
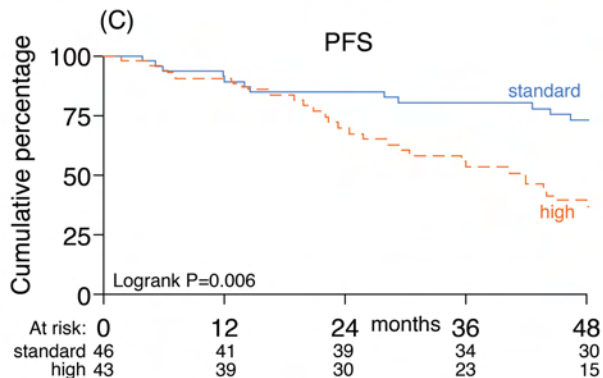
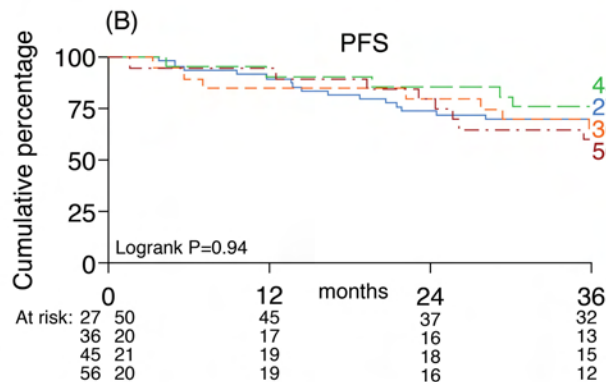
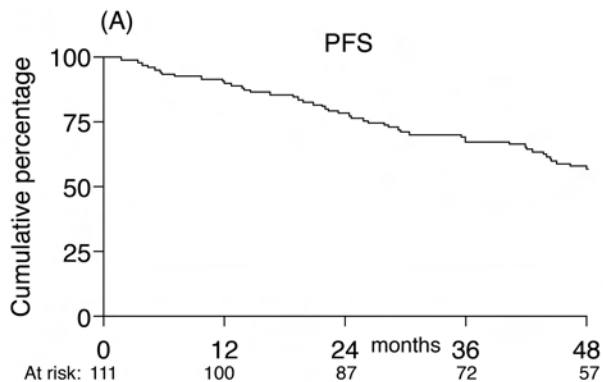
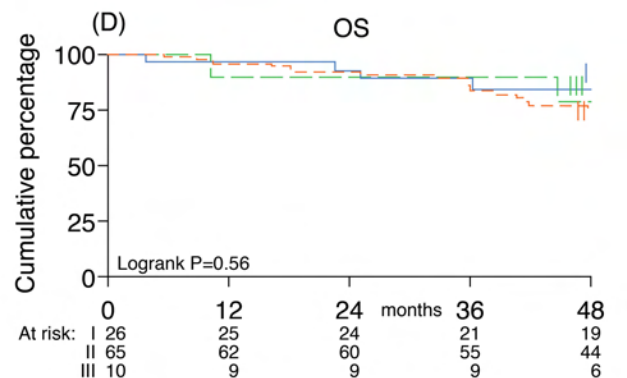
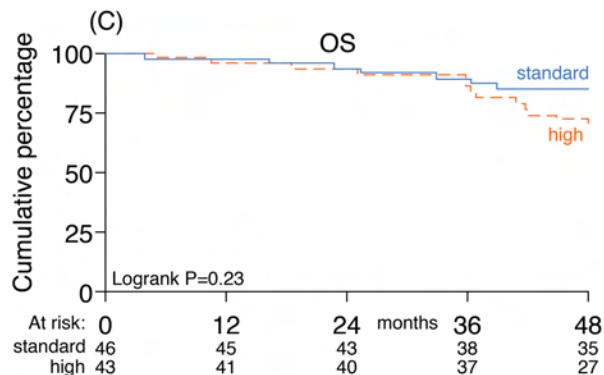
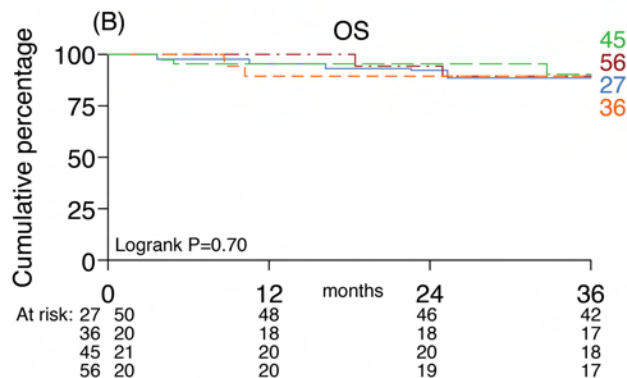
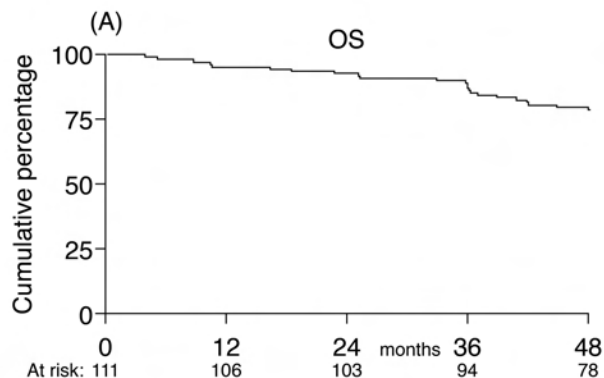


Figure 3



Supplementary data:

Table S1. Treatment-emergent adverse events during therapy.

Toxicity, n (%)	Induction therapy (N=111)		Induction and consolidation therapy (N=111)		SAE
	Any grade	Grade 3/4	Any grade	Grade 3/4	
Hematologic	7 (6)	5 (5)	17 (15)	11 (10)	3 (3)
Anemia	5 (5)	4 (4)	9 (8)	4 (4)	0 (0)
(Febrile) Neutropenia	1 (1)	1 (1)	2 (2)	2 (2)	0 (0)
Thrombopenia	0 (0)	0 (0)	5 (5)	5 (5)	2 (2)
Leukopenia	1 (1)	0 (0)	3 (3)	0 (0)	0 (0)
Other	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)
Non-hematologic	110 (99)	42 (38)	110 (99)	51 (46)	57 (51)
General disorders and administration site conditions	67 (60)	2 (2)	77 (69)	3 (3)	10 (9)
Gastrointestinal disorders	59 (53)	3 (3)	64 (58)	3 (3)	6 (5)
Respiratory, thoracic, and mediastinal disorders	37 (33)	7 (6)	51 (46)	9 (8)	4 (4)
PNP	43 (39)	0 (0)	50 (45)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	43 (39)	9 (8)	45 (41)	10 (9)	2 (2)
Musculature, skeletal, and connective tissue disorders	34 (31)	5 (5)	48 (43)	7 (6)	1 (1)
Vascular disorders	34 (31)	9 (8)	35 (32)	10 (9)	7 (6)
Cardiac disorders	15 (14)	4 (4)	19 (17)	5 (5)	6 (5)
Infections and infestations	26 (23)	2 (2)	47 (42)	6 (5)	12 (11)
Metabolism and nutrition disorders	19 (17)	10 (9)	21 (19)	10 (9)	5 (5)
Investigations	12 (11)	5 (5)	13 (12)	6 (5)	0 (0)
Eye disorders	13 (12)	1 (1)	18 (16)	1 (1)	0 (0)
Psychiatric disorders	8 (7)	0 (0)	12 (11)	0 (0)	0 (0)
Renal and urinary disorders	9 (8)	3 (3)	12 (11)	3 (3)	2 (2)
Endocrine disorders	2 (2)	1 (1)	2 (2)	1 (1)	0 (0)
Surgical and medical procedures	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)
Immune system disorders	3 (3)	2 (2)	4 (4)	2 (2)	1 (1)

Table 1. Treatment-emergent adverse events during induction and consolidation therapy, excluding cyclophosphamide and HDM.

Table S2. Adherence to treatment protocol during induction and consolidation between dose levels.

	Induction				Consolidation			
	20/27 mg/m ²	20/36 mg/m ²	20/45 mg/m ²	20/56 mg/m ²	20/27 mg/m ²	20/36 mg/m ²	20/45 mg/m ²	20/56 mg/m ²
Patients (n)	50	20	21	20	41	15	19	19
Carfilzomib								
Normal completion	29 (58)	13 (65)	12 (57)	15 (75)	29 (71)	8 (53)	14 (74)	10 (53)
Dose delay, reduction and/or interruption	17 (34)	6 (30)	9 (43)	4 (20)	11 (27)	6 (40)	3 (16)	4 (21)
Premature stop	4 (8)	1 (5)	-	1 (5)	1 (2)	1 (7)	2 (11)	5 (26)
Thalidomide								
Normal completion	29 (58)	15 (75)	5 (24)	7 (35)	32 (78)	12 (80)	12 (63)	7 (37)
Dose delay, reduction and/or interruption	15 (30)	4 (20)	14 (67)	10 (50)	3 (7)	-	2 (11)	3 (16)
Premature stop	6 (12)	1 (5)	2 (10)	3 (15)	6 (15)	3 (20)	5 (26)	9 (47)
Dexamethasone								
Normal completion	38 (76)	18 (90)	15 (71)	14 (70)	31 (76)	11 (73)	13 (68)	11 (58)
Dose delay, reduction and/or interruption	8 (16)	1 (5)	6 (29)	5 (25)	8 (20)	3 (20)	4 (21)	3 (16)
Premature stop	4 (8)	1 (5)	-	1 (5)	2 (5)	1 (7)	2 (11)	5 (26)